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间硝苯地平与硝苯地平对肾血管性高血压大鼠血流动力学影响

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Effects of *m*-nifedipine and nifedipine on hemodynamics in renovascular hypertensive rats[1]

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ABSTRACT In the renovascular hypertensive myocardial hypertrophic rats of prevention and regressive groups, the blood pressure was lowered by *m*-nifedipine (*m*-Nif) or nifedipine (Nif) of 20 mg·kg^{-1}·d^{-1}, ig, for 9 wk *vs* control (LVH) group ($P < 0.01$). From the isolated working hearts of prevention and regressive groups, it was found that AP, LVSP, $+dp/dt_{max}$, $-dp/dt_{max}$, CF, and CI values of *m*-Nif and Nif groups increased higher than that of LVH group, but LVEDP and T was lower in *m*-Nif and Nif groups, It was concluded that *m*-Nif exhibits the similar effects like Nif in prevention and reversion of renovascular hypertensive LVH and improvement of hemodynamics.

KEY WORDS *m*-nifedipine; nifedipine; renovascular hypertension; heart hypertrophy; hemodynamics

摘要 间硝苯地平(*m*-Nif)和硝苯地平(Nif)20 mg·kg^{-1}·d^{-1}，ig，9 wk，对大鼠银夹左肾动脉所致肾血管高血压模型能明显降低高血压，预防和逆转肾血管高血压所引起的心肌肥厚. 在离体工作心脏，心肌的收缩和舒张功能及血流动力学参数均得到明显改善，心脏湿重减轻. 表明 *m*-Nif 和 Nif 具有防治高血压心肌肥厚，改善心脏血流动力学的作用.

关键词 间硝苯地平；硝苯地平；肾血管高血压；心肌肥厚；血液动力学

间硝苯地平(*m*-nifedipine，*m*-Nif)为我室研制的1，4二氢吡啶类钙拮抗剂，主要用于抗心肌缺血与降压. 实验证明：*m*-Nif 增加冠状窦氧含量，降低心肌氧摄取率及二氧化碳产生率，使 TT1 明显降低[1]. *m*-Nif 十二指肠给药，显著增加冠脉流量，降低 MVO_2[2]. *m*-Nif 对缺血心肌抑制 CK 释放，部分对抗心肌组织和线粒体钙过负荷，减少心肌镁和钾的丢失[3]. 改善缺血心肌舒张功能强于硝苯地平(nifedipine，Nif)[4,5]. 为了进一步深入分析 *m*-Nif 对肾血管高血压心肌肥厚的预防和逆转作用时心脏血流动力学情况. 本研究采用大鼠肾血管高血压心肌肥厚模型，从离体工作心脏来评定高血压心肌肥厚及药物治疗改善肥厚对心脏泵血功能的影响，并与同类产品 Nif 进行对比.

MATERIALS AND METHODS

Sprague-Dawley 大鼠36只，♂，体重290±*s* 20 g，随机分成6组，采用改良内径0.3 mm 银夹使左肾动脉缩窄方法[6]建立大鼠肾血管高血压心肌肥厚模型，预防组于手术后第6 wk 分别以 *m*-Nif，Nif 20 mg·kg^{-1}·d^{-1}，ig，给药持续9 wk，逆转组于手术后第9 wk（文献报道大鼠术后8 wk 已形成心肌肥厚[6]）分别以 *m*-Nif，Nif 20 mg·kg^{-1}·d^{-1}，ig，给药持续9 wk，假手术组，心肌肥厚组给予等容量 NS，各组分别于用药后第

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9 wk，击昏大鼠开胸取出心脏，制备离体工作心脏[7]，灌流液为改良的 Krebs-Henseleit (KH) 液[8]，用 ST-42型四道生理记录仪(上海医用电子仪器厂产)同步记录主动脉压(AP)、左心室内压(LVSP)，室内压最大变化速率($\pm dp/dt_{max}$)，将 LVSP 信号放大5－10倍，记录左室舒张末期压(LVEDP)，推算等容舒张期心室内压下降的时间常数(T 值)，定时收集1 min 主动脉流出液(AF)和冠脉流出液(CF)，将两者相加得心输出量(CO)，计算每搏输出量(SV)，按 Rubner 公式计算心指数(CI)和每搏指数(SI)，实验完毕，称取左心脏湿重(LVWW)，全部数据以 $\bar{x}\pm s$ 表示，各组间比较用 t 检验.

RESULTS

对血压的影响 预防组 *m*-Nif 和 Nif 于手术后14 wk，血压分别较给药前下降了38±17 %和45±4 % ($P<0.01$)，逆转组 *m*-Nif 和 Nif 于术后17 wk，血压分别较给药前下降了29±17 %和40±10 % ($P<0.01$)，假手术组血压(13.4±0.7 kPa)无显著变化，肥厚组血压于术后第3 wk 持续升高，第6 wk 开始血压直稳定在该水平(24.4±1.5 kPa). 预防组，逆转组血压与肥厚组相比有显著差异($P<0.01$) (Tab 1).

Tab 1. Blood pressure/kPa after *m*-Nif and Nif (20 mg·kg^{-1}·d^{-1}, ig) in consicious (2K1C) Goldblatt hypertensive rats. S: Sham operated; H: Hypertention Hypertrophy; P: Prevention (14 wk); R: Regression (17 wk); 2K1C: Two-kidney one clip; $n=6$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ vs H.

	Normal	Before drug	After drug
S	13.9±0.7	13.8±0.5	13.4±0.7^c
H	14.2±1.5	23.6±2.4	24.4±1.5
P (*m*-Nif)	14.7±1.3	23.0±5.2	13.5±1.0^c
P (Nif)	14.4±0.9	24.4±1.8	13.4±0.5^c
R (*m*-Nif)	14.4±0.9	24.4±1.9	17.1±3.0^c
R (Nif)	13.8±0.8	22.3±2.7	13.2±0.8^c

对离体工作心脏的血流动力学影响

1 对心脏收缩及舒张性能的影响 以 AP、LVSP 和 $+dp/dt_{max}$ 作为反映左室收缩功能指标，以 $-dp/dt_{max}$、LVEDP 和 T 值作为反映左室舒张功能指标，与假手术组比较，肥厚组收缩、舒张功能指标明显降低($P<0.01$)，与肥厚组比较，预防组和逆转组 *m*-Nif 和 Nif 明显改善收缩、舒张功能指标($P<0.01$)，与假手术组比较无显著差异($P>0.05$) (Tab 2).

2 对心脏血流量的影响 与假手术组比较，肥厚组 AF，CF，CO (ml·min^{-1})，SV (ml/stroke)，CI (L·min^{-1}·m^2)，SI (ml·bpm^{-1}·m^2)明显下降($P<0.01$). 与肥厚组比较，预防组和逆转组 m－Nif 和 Nif 能显著改善心脏血流量指标($P<0.01$)，与假手术组比较无显著差异($P>0.05$)(Tab 2).

对心脏湿重的影响 肥厚组 LVWW 与体重(BW)比值(mg·g^{-1})较假手术组显著增加62±20 % ($P<0.01$). 预防组 *m*-Nif 和 Nif LVWW/BW 分别较肥厚组降低33±9 %和33±7 %. 逆转组 *m*-Nif，Nif LVWW/BW 分别降低29±5%和30±11 %($P<0.01$). 预防组略强于逆转组，但无显著差异 ($P>0.05$) (Tab 2).

DISCUSSION

临床及动物实验均已证明钙拮抗剂具有较好的防止和逆转心肌肥厚作用[9－12]. 本研究也发现：(1) 预防量的 *m*-Nif 能明显降低肾血管高血压大鼠血压，防止高血压因压力超负荷引起的 LVH，使心肌收缩及舒张性能及心肌血流量接近正常水平，其结果与钙拮抗剂 Nif 相似，但略强于 Nif. 提示 *m*-Nif 具有预防 LVH 的作用. (2) 治疗量的 *m*-Nif 通过降低高血压，减轻因压力超负荷所引起的 LVH 并能使已肥厚的心肌得以部分逆转，故而显著地改善了 LVH 收缩及舒张性能以及心肌血流动力学. 结果与同类药 Nif 相似，提示 *m*-Nif 具有逆转 LVH，因而改善血流动力学. 本文结果与文献结果[10－12]相符.

Tab 2. Effects of *m*-Nif and Nif (20 mg·kg^{-1}·d^{-1}, ig) on hemodynamics and weight in conscious (2K-1C) Goldblatt hypertensive rat hearts. $n=6$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ vs Hypertrophy.

	Sham operated	Hypertension hypertrophy	Prevention (14 wk) *m*-Nif	Prevention (14 wk) Nif	Regression (17 wk) *m*-Nif	Regression (17 wk) Nif
Heart rate, bpm	248±30^b	193±46	203±43^a	238±20^a	213±30^a	228±33^a
Aortic pressure, kPa	8.9±0.6^c	6.6±0.4	8.2±0.6^c	8.0±0.53^c	8.2±0.7^c	8.5±1.2^c
LVSP, kPa	10.7±1.8^b	8.2±0.4	10.9±1.4^c	10.8±0.9^c	10.8±1.2^c	11.6±1.8^c
LVEDP, kPa	0.50±0.12^c	0.94±0.15	0.59±0.07^c	0.59±0.14^c	0.63±0.09^c	0.36±0.15^c
$+dp/dt_{max}$, kPa·s^{-1}	640±65^c	453±24	574±57^c	553±40^c	608±56^c	645±71^c
$-dp/dt_{max}$, kPa·s^{-1}	407±64^c	219±40	428±19^c	352±30^c	373±29^c	375±53^c
Aortic flow, ml·min^{-1}	39±3.8^a	24±5.4	37±6.1^c	41±1.8^c	40±6.0^c	45±4.9^c
Coronary flow, ml·min^{-1}	11±2.1^c	7.9±0.8	11±2.0^c	11±1.1^c	11±1.9^c	12±1.3^c
Cardiac output, ml·min^{-1}	50±5.1^c	32±5.4	49±6.6^c	52±2.4^c	52±6.0^c	57±5.9^c
Stroke volume, ml	0.21±0.04^c	0.16±0.02	0.25±0.04^c	0.22±0.02^c	0.25±0.02^c	0.25±0.04^c
Cardiac index, L·min^{-1}·m^{-2}	0.96±0.15^c	0.59±0.09	0.91±0.11^c	0.95±0.02^c	1.02±0.17^c	1.07±0.15^c
Stroke index, ml·bpm·m^{-2}	4.0±1.0^c	3.1±0.2	4.3±0.6^c	3.9±0.4^c	5.1±0.4^c	4.8±0.9^c
T, ms	12.5±4.6^c	30.4±3.2	15.9±2.1^c	18.4±2.0^c	18.0±0.6^c	18.4±0.9^c
Body weight (BW), g	438±41^a	439±26	443±32^a	456±24^a	410±40^a	444±52^a
Heart wet weight (HWW), g	1.32±0.14^c	1.71±0.11	1.47±0.12^c	1.49±0.05^c	1.29±0.14^c	1.32±0.14^c
LVWW, g	0.51±0.05^c	0.83±0.11	0.55±0.06^c	0.57±0.04^c	0.54±0.04^c	0.57±0.06^c
SVWW, g	0.39±0.07^a	0.47±0.06	0.45±0.03^a	0.43±0.05^a	0.40±0.05^a	0.40±0.05^a
HWW/BW, mg·g^{-1}	3.01±0.18^c	3.89±0.34	3.31±0.08^c	3.28±0.17^c	3.15±0.15^c	2.99±0.41^c
LVWW/BW, mg·g^{-1}	1.17±0.16^c	1.87±0.14	1.24±0.10^c	1.24±0.07^c	1.33±0.11^c	1.30±0.18^c
SVWW/BW, mg·g^{-1}	0.89±0.13^a	1.07±0.14	1.01±0.05^a	0.93±0.08^a	0.97±0.07^a	0.91±0.12^a

LVSP: Left ventricular systomic pressure; T: Time constant of isovolumic diastolic pressure decay; LVWW: Left ventricular wet weight; SVWW: Septum ventricular wet weight.

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263—266

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地尔硫䓬缓释片在不同肾功能高血压患者中的药物动力学和药效学

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Pharmacokinetics and pharmacodynamics of slow release tablet of diltiazem in hypertensive patients with various renal functions

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ABSTRACT Twenty hypertensive patients were equally divided into 2 groups: A) with normal renal function (NRF) and B) with impaired renal function (IRF) according to creatinine clearance, blood urea nitrogen and creatinine levels. The pharmacokinetic and pharmacodynamic effects of diltiazem (Dil, 90 mg, bid × 7 d, *po*) were studied. The pharmacokinetic parameters in IRF patients (K_a 0.7±0.2 h^{-1}, $T_{\frac{1}{2}e}$ 3.7±0.7 h, C_{max_1} 45±4 ng·ml^{-1}, T_{max_1} 3.1±0.4 h) did not differ from those in NRF patients (0.7±0.5 h^{-1}, 4.1±1.3 h, 41±5 ng·ml^{-1} and 3.4±0.4 h, $P > 0.05$). Antihypertensive efficacy of Dil in patients with IRF was similar to that in those with NRF, and the hypotensive effect lasted over 24 h. The plasma Dil concentrations were strongly correlated with a decrease in BP in both groups. It was concluded that IRF did not affect the disposition of slow release Dil tablet under a steady state. No dosage adjustment of Dil is necessary in hypertensive patients with IRF.

KEY WORDS diltiazem; delayed-action preparations; pharmacokinetics; blood pressure; kidney function tests

摘要 肾功能正常和受损两组高血压病人作diltiazem 缓释片7 d (Dil, 90 mg, bid)的药动学和药效学研究. 结果：两组病人的主要药动学参数 K_a, K_e, $T_{\frac{1}{2}a}$, $T_{\frac{1}{2}e}$, C_{max}和 T_{max}相比较无显著性差异. 降压幅度相同，降压作用达24 h，血药浓度与血压变化呈正相关. 因此，肾功能损害并不影响 Dil 缓释片稳态期的体内消除过程，无需调整剂量.

关键词 地尔硫䓬；迟效制剂；药物动力学；血压；肾功能试验

地尔硫䓬(diltiazem, Dil)用于高血压治疗日趋广泛[1]. 其降压作用长，不良反应轻且服用方便的缓释剂型也已问世[2,3]. Dil 缓释片是一种新剂型[4]，我们曾报道了该药在正常人中的药动学和药效学[5]，本文进一步对肾功能

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